REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1, 6-8 and 69 are currently pending.

II. Prior Rejections

Applicants acknowledge the withdrawal of prior rejections under 35 U.S.C. §§101 and 112, second paragraph.

III. Claim Rejection under 35 USC 112, First Paragraph

Claims 1, 6, 8, and 69 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Action asserts that the specification does not provide any teaching showing how the antibody dCK conjugate enters the nucleus and phosphorylates nucleoside located inside the nucleus of the cell.

In response to Applicants' arguments, the Action acknowledges that nucleoside analog AraC is phosphorylated in the cytoplasm by cytosolic dCK. However, the Action nevertheless asserts that "the antibody conjugate as treatment agent is required to be penetrated into nucleus in order to perform the function and be used by one skilled in the art for treating a tumor." Applicants traverse the rejection.

In analyzing the claims under 35 USC §112, first paragraph, the initial burden is on the Examiner to establish a *prima facie* showing of non-enablement. (MPEP §2164.04) Under 35 USC §112 and Patent Office rules, Applicants' assertion of enablement in the specification must be accepted, unless the Examiner can make out a *prima facie* case of non-enablement. The test for enablement is whether the specification teaches one of skill in the art how to make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (fed. Cir. 1988). The factors to be considered are summarized in *Wands*, which include: (a) the breadth of the claim; (b) the nature of the invention; (c) the state of the prior art; (d) the level of skill of one of ordinary skill in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make and use the invention based on the content of the disclosure. (MPEP §2164.01(a))

The state of the art teaches one of skill in the art that native dCK exerts its function in the cytoplasm, in consistent with the instant disclosure. For example, Zhu *et al.* teaches that cytosolic dCK phosphorylates nucleoside analogs. (Zhu *et al.* 2000, J. Biol. Chem. 275:26727-31, cited in the Office Action dated December 27, 2006) Further, Applicants herewith submit a Declaration by Dr. Arnon Lavie pursuant to 37 C.F.R. §1.312. In the Declaration, Dr. Lavie testified that it has been known that native human dCK resides in the cytoplasm, and that nuclear localization of dCK is likely an artifact of over-expression of the protein by transfection. Additionally, Dr. Lavie testified that dCK performs its physiological function in the cytoplasm. See paragraphs 5-8 of the Declaration.

Applicants submit that the Action has not established a *prima facie* showing of non-enablement. The specification teaches, and the Action apparently does not dispute, that the antibody dCK conjugate enters into the cytoplasm of the cell. Thus, the antibody brings genetically modified dCK to the cytoplasm, the compartment where the native enzyme exerts its physiological function. While acknowledging that nucleoside analogs are phosphorylated by dCK in the cytoplasm, the Action has not provided <u>any reasoning</u> for its assertion that the <u>antibody dCK conjugate</u>, as a treatment agent, nevertheless "is required to be penetrated into nucleus" in order to perform its function. Without showing any evidence contradicting the state of the art, the Action has failed to establish a *prima facie* showing of non-enablement.

The Action further asserts that Figures 6-9 in the specification do not demonstrate any additional effect of the antibody dCK conjugate and AraC on cell killing compared with the effect of AraC alone. Applicants respectfully submit that the Action may have misconstrued the results shown in the figures. Although the figures are self-explanatory, Applicants nevertheless provide further clarification by Dr. Lavie as set forth in the Declaration. See paragraphs 9-14 of the Declaration. In summary, Dr. Lavie testified that the combinatorial treatment of AraC <u>and</u> the conjugate results in increased cell death in CD33 positive cells by about 20% (Figure 6), 30% (Figure 8), or 70% (Figure 7) comparing to cells treated with AraC alone. Thus, the specification does show additional effects of the combination of antibody dCK conjugate and AraC.

The Action is correct in that data presented in Figure 9 do not show significant difference in the levels of cell death in the cells treated with AraC alone or AraC plus the conjugate. The negative results are expected, however, because 293 cells used in this

experiment do not express CD33. See page 85 of the specification. As a result, the conjugate could not be targeted to the cells to exert its effect. The data shown in Figure 9 is consistent with the effects observed with the conjugate in inducing further cell death in CD33 expressing cells. Thus, the specification provides ample examples that teach one of skill in the art how to make and use the claimed invention.

Based on the foregoing, Applicants respectfully submit that the Action has not established a *prima facie* case of non-enablement and request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

CONCLUSION

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended or as originally presented. Allowance of the claims is thereby respectfully solicited.

If there are any questions or comments regarding this Response, the Patent Office is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

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